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(54) Title: CALCILYTIC COMPOUNDS

(57) Abstract

Novel arylalkylamino compounds exhibiting calcilytic properties are provided.

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CALCILYTIC COMPOUNDS

FIELD OF INVENTION

The present invention relates to novel arylalkylamine calcilytic compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.

In mammals, extracellular Ca^{2+} is under rigid homeostatic control and regulates various processes such as blood clotting, nerve and muscle excitability, and proper bone formation. Extracellular Ca^{2+} inhibits the secretion of parathyroid hormone ("PTH") from parathyroid cells, inhibits bone resorption by osteoclasts, and stimulates secretion of calcitonin from C-cells. Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular Ca^{2+} concentration.

PTH is the principal endocrine factor regulating Ca^{2+} homeostasis in the blood and extracellular fluids. PTH, by acting on bone and kidney cells, increases the level of Ca^{2+} in the blood. This increase in extracellular Ca^{2+} then acts as a negative feedback signal, depressing PTH secretion. The reciprocal relationship between extracellular Ca^{2+} and PTH secretion forms an important mechanism maintaining bodily Ca^{2+} homeostasis.

Extracellular Ca^{2+} acts directly on parathyroid cells to regulate PTH secretion. The existence of a parathyroid cell surface protein which detects changes in extracellular Ca^{2+} has been confirmed. See Brown *et al.*, *Nature 366*:574, 1993. In parathyroid cells, this protein, the calcium receptor, acts as a receptor for extracellular Ca^{2+}, detects changes in the ion concentration of extracellular Ca^{2+}, and initiates a functional cellular response, PTH secretion.

Extracellular Ca^{2+} influences various cell functions, reviewed in Nemeth *et al.*, *Cell Calcium 11*:319, 1990. For example, extracellular Ca^{2+} plays a role in parafollicular (C-cells) and parathyroid cells. See Nemeth, *Cell Calcium 11*:323, 1990. The role of extracellular Ca^{2+} on bone osteoclasts has also been studied. See Zaidi, *Bioscience Reports 10*:493, 1990.

Various compounds are known to mimic the effects of extra-cellular Ca^{2+} on a calcium receptor molecule. Calcilytics are compounds able to inhibit calcium receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca^{2+}. Calcilytics are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators which are active at

Ca^{2+} receptors. Such calcilytics are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides such as hormones, enzymes or growth factors, the expression and/or secretion of which is regulated or affected by activity at one or more Ca^{2+} receptors. Target diseases or disorders for calcilytic compounds include diseases involving abnormal bone and mineral homeostasis.

Abnormal calcium homeostasis is characterized by one or more of the following activities: an abnormal increase or decrease in serum calcium; an abnormal increase or decrease in urinary excretion of calcium; an abnormal increase or decrease in bone calcium levels (for example, as assessed by bone mineral density measurements); an abnormal absorption of dietary calcium; an abnormal increase or decrease in the production and/or release of messengers which affect serum calcium levels such as PTH and calcitonin; and an abnormal change in the response elicited by messengers which affect serum calcium levels.

Thus, calcium receptor antagonists offer a unique approach towards the pharmacotherapy of diseases associated with abnormal bone or mineral homeostasis, such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis.

SUMMARY OF THE INVENTION

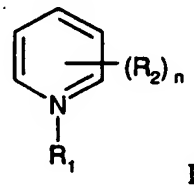
The present invention comprises arylalkylamine derivatives represented by Formula (I) hereinbelow and their use as calcium receptor antagonists which are useful in the treatment of a variety of diseases associated with abnormal bone or mineral homeostasis, including but not limited to hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis.

The present compounds maintain calcium receptor activity while exhibiting increased stability as compared to other calcium receptor antagonists.

The present invention further provides a method for antagonizing calcium receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I), indicated hereinbelow.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are selected from Formula (I) hereinbelow:



Formula (I)

wherein;

n is an integer from 0 to 3;

R_1 is selected from the group consisting of R_3, and CH_2YR_3 wherein R_3 is C_{1-15} aryl or C_{1-20} alkyl and Y is selected from the group consisting of CONH, COO, CONHNHCO and CO;

R_2 is selected from the group consisting of R_3, $CONHR_3$, H, OR_3, X, $N(R_3)_2$, $CON(R_3)_2$, COR_3, and SR_3, wherein R_3 is H, C_{1-15} aryl or C_{1-20} alkyl.

Preferably, n is 1 and the R_2 moiety is beta to the N heteroatom. When n is 2, the R_2 moiety is alpha or gamma to the N heteroatom.

Preferably, R_1 is CH_2YR_3.

Preferably, Y is CONH or COO.

Preferably, R_2 is $CONHR_3$.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1-20 carbon atoms joined together. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. The substituents are selected from F, Cl, Br, I, N, S and O. Preferably, no more than three substituents are present. More preferably, the alkyl has 1-12 carbon atoms and is unsubstituted. Preferably, the alkyl group is linear. Preferably, the alkyl group is saturated.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi- electron system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The substituents are selected from F, Cl, Br, I, N, S and O. Preferably, the aryl is either optionally substituted phenyl,or optionally substituted 2-naphthyl. Preferably, the aryl group is unsubstituted. The most preferred aryl group is unsubstituted phenyl.

Preferred compounds useful in the present invention include:

3-Carbamoyl-1-((dodecylcarbamoyl)methyl)pyridinium, chloride

4,4'-Biphenacylene-bis(pyridiniumbromide),

3-(Dodecylcarbamoyl)-1-methylpyridinium, bromide,

1-(((Dodecyloxy)carbonyl)methyl)-3-(methylcarbamoyl)pyridinium, chloride,

4-Carbamoyl-1-((dodecyloxycarbonyl)methyl)pyridinium, chloride,

3-Carbamoyl-1-((dodecyloxycarbonyl)methyl)pyridinium, chloride,

1-((Decyloxycarbonyl)methyl)3-carbamoyl-pyridinium, chloride,

1-((Decyloxycarbonyl)methyl)-4-carbamoylpyridinium, chloride,

1-((Decylcarbamoyl)methyl)-3-carbamoylpyridinium, chloride,

1-((Dodecylcarbamoyl)methyl)-3-(phenylcarbamoyl)pyridinium, chloride,

1-(Tetradecanoylhydrazinocarbonylmethyl)pyridinium chloride,

1-Methyl-2-(decylcarbamoyl)pyridinium iodide,

2-(4-(4-Dimethylamino)phenyl)-1,3-butadiene-1-yl)-ethylpyridinium perchlorate,

3-Carbamoyl-1-undecylpyridinium bromide, and

1-((Decylcarbamoyl)methyl)-4-carbamoylpyridinium chloride.

More preferred compounds useful in the present invention include:

3-Carbamoyl-1-((dodecylcarbamoyl)methyl)pyridinium, chloride,

3-(Dodecylcarbamoyl)-1-methylpyridinium, bromide,

4-Carbamoyl-1-((dodecyloxycarbonyl)methyl)pyridinium, chloride,

3-Carbamoyl-1-((dodecyloxycarbonyl)methyl)pyridinium, chloride,

1-((Decyloxycarbonyl)methyl)3-carbamoyl-pyridinium, chloride, and

1-((Dodecylcarbamoyl)methyl)-3-(phenylcarbamoyl)pyridinium, chloride.

The most preferred compound useful in the present invention is

3-Carbamoyl-1-((dodecylcarbamoyl)methyl)pyridinium, chloride.

The present compounds can also be formulated as pharmaceutically acceptable salts and complexes thereof. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid,

ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

The present invention provides compounds of Formula (I) above which can be prepared using standard techniques. An overall strategy for preparing preferred compounds described herein can be carried out as described in this section. The examples which follow illustrate the synthesis of specific compounds. Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other compounds of the present invention.

All reagents and solvents were obtained from commercial vendors. Starting materials (e.g., amines and epoxides) were synthesized using standard techniques and procedures.

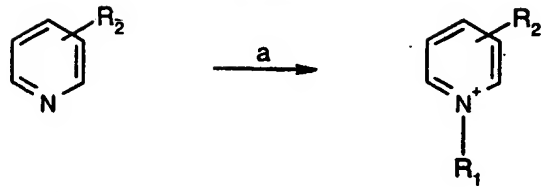
A general procedure used to synthesize many of the present compounds is as follows:

The preparation of the compounds described herein either follows previously reported procedures or was accomplished according to the methods illustrated below. An overall strategy for preparing preferred compounds described herein can be carried out as described in this section. The examples which follow illustrate the synthesis of specific compounds. Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other Formula (I) compounds.

All reagents and solvents are obtained from commercial vendors. Starting materials are synthesized using standard techniques and procedures.

A general procedure used to synthesize many of the compounds was carried out as indicated in Scheme 1 below. A solution of the substituted pyridine (e.g. nicotinamide, 1 mmol) and excess alkylating agent (e.g. N-dodecyl-2-chloroacetamide, 2 mmol) in nitromethane or similar solvent (2 mL) is stirred for 24h at 90-100°C. Typically upon cooling, the pyridinium salt precipitates out of solution and the corresponding salt is collected.

Scheme 1



a. BrR_1, NO_2CH_3, 90-100°C, 24h

With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The calcilytic compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, *e.g.*, intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various calcilytic compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts admininstered also depend on the routes of admininstration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be admninstered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be admininstered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula(I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "modulator" means antagonist.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH),

cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (*e.g.*, aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.

In a preferred embodiment of the present invention, the present compounds are used to increase serum parathyroid ("PTH") levels. Increasing serum PTH levels can be helpful in treating diseases such as hypoparathyroidism, osteosarcoma,, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and osteoporosis.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way,

with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

(I) Calcium Receptor Inhibitor Assay

Calcilytic activity was measured by determining the IC_{50} of the test compound for blocking increases of intracellular Ca^{2+} elicited by extracellular Ca^{2+} in HEK 293 4.0-7 cells stably expressing the human calcium receptor. HEK 293 4.0-7 cells were constructed as described by Rogers *et al., J. Bone Miner. Res. 10* Suppl. 1:S483, 1995 (hereby incorporated by reference herein). Intracellular Ca^{2+} increases were elicited by increasing extracellular Ca^{2+} from 1 to 1.75 mM. Intracellular Ca^{2+} was measured using fluo-3, a fluorescent calcium indicator.

The procedure was as follows:

1. Cells were maintained in T-150 flasks in selection media (DMEM supplemented with 10% fetal bovine serum and 200 ug/mL hygromycin B), under 5% CO_2:95% air at 37 °C and were grown up to 90% confluency.

2. The medium was decanted and the cell monolayer was washed twice with phosphate-buffered saline (PBS) kept at 37 °C. After the second wash, 6 mL of 0.02% EDTA in PBS was added and incubated for 4 minutes at 37 °C. Following the incubation, cells were dispersed by gentle agitation.

3. Cells from 2 or 3 flasks were pooled and pelleted (100 x g). The cellular pellet was resuspended in 10-15 mL of SPF-PCB+ and pelleted again by centrifugation. This washing was done twice.

Sulfate- and phosphate-free parathyroid cell buffer (SPF-PCB) contains 20 mM Na-Hepes, pH 7.4, 126 mM NaCl, 5 mM KCl, and 1 mM $MgCl_2$. SPF-PCB was made up and stored at 4 °C. On the day of use, SPF-PCB was supplemented with 1 mg/mL of

D-glucose and 1 mM $CaCl_2$ and then split into two fractions. To one fraction, bovine serum albumin (BSA; fraction V, ICN) was added at 5 mg/mL (SPF-PCB+). This buffer was used for washing, loading and maintaining the cells. The BSA-free fraction was used for diluting the cells in the cuvette for measurements of fluorescence.

4. The pellet was resuspended in 10 mL of SPF-PCB+ containing 2.2 uM fluo-3 (Molecular Probes) and incubated at room temperature for 35 minutes.

5. Following the incubation period, the cells were pelleted by centrifugation. The resulting pellet was washed with SPF-PCB+. After this washing, cells were resuspended in SPF-PCB+ at a density of 1-2 x 106 cells/mL.

6. For recording fluorescent signals, 300 uL of cell suspension were diluted in 1.2 mL of SPF buffer containing 1 mM $CaCl_2$ and 1 mg/mL of D-glucose. Measurements of fluorescence were performed at 37 °C with constant stirring using a spectrofluorimeter. Excitation and emission wavelengths were measured at 485 and 535 nm, respectively. To calibrate fluorescence signals, digitonin (5 mg/mL in ethanol) was added to obtain F_{max}, and the apparent F_{min} was determined by adding Tris-EGTA (2.5 M Tris-Base, 0.3 M EGTA). The concentration of intracellular calcium was calculated using the following equation:

Intracellular calcium = $(F\text{-}F_{min}/F_{max})$ x Kd; where Kd = 400 nM.

7. To determine the potential calcilytic activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca^{2+} from 1 to 2mM. Calcilytic compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca^{2+} elicited by extracellular Ca^{2+}.

In general, those compounds having lower IC_{50} values in the Calcium Receptor Inhibitor Assay are more preferred compounds. Compounds having an IC_{50} greater than 50 uM were considered to be inactive. Preferred compounds are those having an IC_{50} of 10uM or lower, more preferred compounds have an IC_{50} of 1uM, and most preferred compounds have an IC_{50} of 0.1uM or lower.

(II) Calcium Receptor Binding Assay

HEK 293 4.0-7 cells stably transfected with the Human Parathyroid Calcium Receptor("HuPCaR") were scaled up in T180 tissue culture flasks. Plasma membrane is obtained by polytron homogenization or glass douncing in buffer (50mM Tris-HCl pH 7.4, 1mM EDTA, 3mM $MgCl_2$) in the presence of a protease inhibitor cocktail containing 1uM

Leupeptin, 0.04 uM Pepstatin, and 1 mM PMSF. Aliquoted membrane was snap frozen and stored at -80°C. ^3H labeled compound was radiolabeled to a radiospecific activity of 81Ci/mmole and was aliquoted and stored in liquid nitrogen for radiochemical stability.

A typical reaction mixture contains 2 nM ^3H compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-naphthyl)ethylamine), 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume of 0.5 mL. Incubation is performed in 12 x 75 polyethylene tubes in an ice water bath. To each tube 25 uL of test sample in 100% EtOH is added, followed by 400 uL of cold incubation buffer, and 25 uL of 20 nM ^3H-compound in 100% EtOH. The binding reaction is initiated by the addition of 50 uL of 80-200 ug/mL HEK 293 4.0-7 membrane diluted in incubation buffer, and allowed to incubate at 4°C for 30 min. Wash buffer is 50 mM Tris-HCl containing 0.1% PEI. Nonspecific binding is determined by the addition of 100-fold excess of unlabeled homologous ligand, and is generally 30% of total binding. The binding reaction is terminated by rapid filtration onto 1% PEI pretreated GF/C filters using a Brandel Harvestor. Filters are placed in scintillation fluid and radioactivity assessed by liquid scintillation counting.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

EXAMPLE 1

2-(Decylcarbamoyl)-1-methylpyridinium iodide:

a) N-Decylpicolinamide:

A mixture of picolic acid (1.0 g, 8.1 mmole), decylamine (1.28 g, 8.1 mmole), HOBT.H_2O (1.31 g, 9.7 mmole), diisopropylethylamine (2.10 g, 16.2 mmole), and EDC (2.89 g, 9.7 mmole) in dried acetonitrile (15 mL) was stirred at room temperature for 14h. The mixture was concentrated, taken up in H_2O, extracted with ethyl acetate (3x). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to afford an light brown oil 2.00 g, 94%. ^1H-NMR (250 MHz, $CDCl_3$) d 0.88 (t, J = 4.3 Hz, 3H); 1.40 (m, 14H); 1.65 (m, 2H); 3.45 (q, J = 4.3 Hz, 2H); 7.40 (ddd, J = 1.1, 4.8, 9.6 Hz, 1H); 7.85 (ddd, J = 1.1, 4.8, 9.6 Hz, 1H); 8,10 (s, 1H); .8 Hz, 1H); 8.54 (dd, J = 0.95 Hz, 2.91 Hz, 1H).

b) 2-(N-Decylcarboxamidyl)-1-methylpyridinium iodide:

A mixture of N-decylpicolinamide (0.41 g, 1.5 mmole) and methyl iodide (1.02 g, 7.8 mmole) in anhydrous p-dioxane (5 mL) was refluxed for 12h. The mixture was cooled

and concentrated to dryness. The residue was triturated with acetone/ether to afford white solid (0.11 g, 17%). ^{1}H-NMR (250 MHz, DMSO-d_6): d 0.88 (t, J = 4.3 Hz, 3H); 1.45 (m, 14H); 1.65 (m, 2H); 3.40 (q, J = 4.3 Hz, 2H); 4.30 (s, 3H); 8.20 (d, J = 4.8 Hz, 1H); 8.25 (t, J = 4.8 Hz, 8.70 (t, J = 4.8 Hz, 1H); 9.10 (d, J = 4.8 Hz, 1H); 9.25 (s, 1H). IR (KBR, cm^{-1}): 3430, 3209, 3050, 2900, 1673, 1623, 1552, 1461, 1455, 1316, 1286. Anal. Calcd for $C_{17}H_{29}IN_2O.0.50\ H_2O$: C, 49.40; H, 7.32; N, 6.78); Found: C, 49.51; H, 7.11; N, 6.85.

EXAMPLE 2

3-Carbamoyl-1-[(dodecylcarbamoyl)methyl]pyridinium, chloride

a) N-Dodecyl-2-chloroacetamide

To a stirred, cooled mixture of n-decylamine (13.93 g, 88.5426 mmole), and triethylamine (8.96 g, 88.5426 mmole) in dried THF (100mL) was added chloroacetyl chloride (10.0 g, 88.5426 mmole) dropwise. After stirring at 0^{0}C in 1h, the mixture was quenched by H_2O, and extracted with EtOAc (3x). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a light brown solid which was triturated in pentane to afford an off white solid (15.52 g, 75%). ^{1}H-NMR (250 MHz, $CDCl_3$) d : 6.50 (s, 1H), 3.89 (s, 2H), 3.30 (q, J = 6.6 Hz, 2H), 1.56 (m, 2H), 1.30 (m, 18H), 0.88 (t, J = 6.6 Hz, 3H).

b) 3-Carbamoyl-1-[(dodecylcarbamoyl)methyl]pyridinium, chloride

A mixture of nicotinamide (0.77 g, 6.3 mmole), and N-dodecyl-2-chloroacetamide (2.9 g, 12.6 mmole) in nitromethane (15 mL) was refluxed for 24h. The mixture was cooled, and the solid thus obtained was filtered and triturated in acetone/EtOAc to give a light yellow solid (0.83 g, 37%). MS (ES) m/e 348.2 (M^+) ^{1}H-NMR (400 MHz, DMSO-D_6) d: 9.40 (s, 1H), 9.03 (d, J =7.1Hz, 1H), 8.98 (d, J =7.3Hz, 1H), 8.60(bs, 2H, NH_2), 8.22 (dd, J=7.3, 7.1 Hz, 1H), 8.1 (bs, 1H, NH), 5.2 (s, 2H), 3.05- 3.11 (m, 2H), 1.39-1.48 (m, 2H),2.16-2.25 (m, 18H), 0.82 (t, J=6.5 Hz, 3H).

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

EXAMPLE 3

Inhalant Formulation

A compound of Formula (I) (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

EXAMPLE 4

Tablet Formulation

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. (I))	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

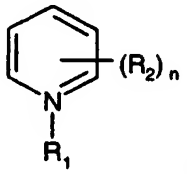
EXAMPLE 5

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of Formula (I) in polyethylene glycol with heating. This solution is then diluted with water for injections (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

What is claimed is:

1. A method of antagonizing a calcium receptor which comprises administering to a subject in need thereof, an effective amount of a compound having the structure of Formula (I):



(I)

wherein;

n is an integer from 0 to 3;

R_1 is R_3 or CH_2YR_3 wherein R_3 is C_{1-15} aryl or C_{1-20}alkyl and Y is selected from the group consisting of CONH, COO, CONHNHCO and CO; and

R_2 is selected from the group consisting of R_3, $CONHR_3$, H, OR_3, X, $N(R_3)_2$, $CON(R_3)_2$, COR_3, and SR_3, wherein R_3 is H, C_{1-15} aryl or C_{1-20} alkyl,

or a pharmaceutically acceptable salt thereof.

2. A method according to claim 1 wherein n is 1.

3. A method according to claim 2 wherein R_3 is unsubstituted phenyl or C_{1-12} linear, unsubstituted , saturated alkyl.

4. A method according to claim 3 wherein Y is CONH or COO.

5. A method according to claim 4 wherein R_3 is methyl.

6. A method according to claim 2 wherein R_1 is CH_2YR_3.

7. A method of treating a disease or disorder characterized by an abnormal bone or mineral homeostasis, which comprises administering to a subject in need of treatment thereof an effective amount of a compound of claim 1.

8. A method according to claim 7 wherein the bone or mineral disease or disorder is selected from the group consisting of osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and osteoporosis.

9. A method according to claim 8 wherein the bone or mineral disease or disorder is osteoporosis.

10. A method of increasing serum parathyroid levels which comprises administering to a subject in need of treatment an effective amount of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/06618

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44
US CL :514/355
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/355

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, CAOLD, CA, MEDLINE, WPIDS, EMBASE- compounds herein for any purpose.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem. abstr., Vol. 54, 1959, (Columbus, OH, USA) column 4631, '3-Carbamoylpyridinium chlorides', GB 822,351 (CILAG LTD.), 21 October 1959.	1-10
A	VAN ESCH, J.H. et al. Reduction of Nicotinamides, Flavins, and Manganese Porphyrins by Formate, Catalyzed by Membrane-Bound Rhodium Complexes. J. Org. Chem. 1995, Vol. 60, No. 6, pages 1599-1610.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 JUNE 1998	Date of mailing of the international search report 30 JUL 1998
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